REMARKS

The only issue outstanding in the office action of December 21, 2009, is the single rejection of all claims under 35 U.S.C. 103. Reconsideration of this issue, in view of the following discussion, is respectfully requested.

Claims 1, 3-5 and 9-16 are now rejected under 35 U.S.C. 103 over Reynolds (USP 3,808,332) taken with Jacobs (US 2005/0003491). As will be recalled, Reynolds discloses a pharmaceutical composition comprising a carrier and the reaction product of tertiary phosphine with thyroxine and 3, 5, 3'-L-triiodothyronine. The Office Action admits, at page 3, that Reynolds fails to teach gelatin in the combination. There are additional significant differences between the disclosure of Reynolds and the present claims. For example, the office action cites column 7, lines 65-67 for the argument that "no organic solvent is present." This conclusion, however, is unfounded. The noted portion of Reynolds discloses that the "combinations used in this evaluation [of L-thyroxine and L-triiodothyronine] were prepared by physically admixing various amounts" of the compounds. Simply reciting that the compounds are in "physical admixture" means only that the compounds are physically admixed – nothing more. This disclosure does not mean, as apparently taken in the office action, that the mixture is "free of organic solvent". Moreover, it is clear that the opposite is true. Page 2 of the office action refers to composition I and J at column 7. However, the compositions are used therein to produce tablets in a process in which the ingredients are "granulated with a "alcoholic solution of polyvinylpyrrolidone." See col. 7, lines 14 and 15, 33 and 34. Thus, the materials are not "free of organic solvent." Thus, Reynolds contains several significant deficiencies verses the present claims.

Jacobs, cited at page 3 of the office action for the argument that it would be obvious to use gelatin in the solid formulations of Reynolds,, would not be employed in this manner by one of ordinary skill in the art. Jacobs et al. deals with secreted *proteins* and *polynucleotides* encoding them. See page 174, paragraph 4072. Jacobs is silent regarding thryroxin or levo-thyroxin. Beginning on page 174 Jacobs discloses numerous administration routes and dosage forms. For example, the compositions of Jacobs may be administered topically, systematically, or locally as an implant or device. They may be administered by intravenous, cutaneous or

subcutaneous injection. The compositions may be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition may additionally contain a solid "carrier," such as a gelatin or an adjuvant. Thus, Jacobs broadly discloses numerous administration routes and dosage forms, none of which deal with thryroxin or levo-thyroxin. A skilled worker dealing with the problem of stabilization of levo-thyroxin would simply not look towards a broad generic disclosure that deals with numerous administration forms of entirely different proteins for guidance.

However, the rejection argues that gelatin is "conventionally employed as a binder in tablet formations because of its well-established cohesive qualities." It is respectfully submitted, however, that it is an oversimplification of the pharmaceutical composition arts to argue, as done in the office action, that it would be obvious to employ gelatin in any solid or tablet formation. In fact, these formations are typically individualized for the specific ingredients employed therein. The fact that there is no disclosure of the particular active ingredients claimed herein with the use of gelatin, along with a well-known stabilization problem for the use of the active materials, suggests that the opposite is true. Page 174, paragraph 4072, relied on in the office action, in fact discloses that a *protein* may be formulated, *inter alia*, as a tablet and that such tablet may contain as a solid "carrier" gelatin. In the present invention the active ingredient is not a protein but a small molecule and gelatin is used in the present invention as claimed as a binder. Jacobs does not contain any teaching or hint that gelatin may improve the stability of an active ingredient, neither for a protein (which is totally different from the active ingredient of the present invention) nor for any other one (in fact the whole disclosure of Jacobs is limited to proteins (see, for example, paragraph [0013] on page 1). One of ordinary skill in the art would simply not take a teaching relevant to fragile proteins and combine it with very different small molecule compounds.

It is again respectfully maintained that the two declarations of record further establish the non-obviousness, and thus patentability, of the present claims. In the first Declaration, comparison is made between a formulation containing gelatin, and one containing the polymer HPMC, (hydroxypropylmethylcellulose). The declaration shows that, unexpectedly, where gelatin is substituted for HPMC as a binder, active agent content over time is significantly greater

for compositions formulated with gelatin then the active agent content maintained for those formulated with HPMC. One of ordinary skill in the art would not expect such a beneficial and significant stability effect for gelatin, as nowhere in the cited references is any advantage taught for gelatin; gelatin is simply a conventional bulk carrier for other agents. In the second Declaration it is shown that a formulation according to the invention, which contains a small amount (2.50 mg) of gelatin as binder has a better stability than the same formulation containing 3.50 mg HPMC, which is the most frequently used binder. The improvement of stability further increases with the amount of gelatin in a dose-dependent way.

It is accordingly respectfully maintained that the declarations show unexpected results. The Examiner expresses doubt but does not provide any evidence, facts or reasoning sufficient to justify her allegation that hydroxypropyl methylcellulose might impart a de-stabilizing effect. All evidence is to the contrary. The Office Action simply does not provide sufficient basis in support of a *reasonable* doubt on this issue. It is well established principle of law that, where the USPTO seeks to rely on a chemical theory in order to support a rejection, the USPTO must provide evidence supporting that theory. See *In re Grose*, 592 F.2d 1161, 201 USPQ 57 (CCPA 1979). No evidence supporting the theory that HPMC would destabilize a tablet preparation has been provided herewith, and instead, it is submitted that the assumption would be to the contrary as HPMC is a conventional binder used in tablets.

It is clearly shown by the data provided in the declarations of Dr. Schaffler and Dr. Lindenblatt that gelatin unexpectedly increases the stability of the formulation. The improvement in stability increases with the amount of gelatin. This alone clearly proves the stabilizing effect of gelatin, and is enough to establish non-obviousness. Even if HPMC were a destabilizer (not established) this would not affect the unexpectedness of including gelatin to enhance stability.

Accordingly, withdrawal of all rejections of record is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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